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(54) Title: PRESERVATIVE BLENDS CONTAINING QUATERNARY AMMONIUM COMPOUNDS

(57) Abstract: The present invention provides a biocidal composition comprising a synergistic mixture of certain quaternary ammonium biocides and one or more ketone acids, aromatic carboxylic acids, salts thereof, or mixtures thereof.

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PRESERVATIVE BLENDS CONTAINING QUATERNARY AMMONIUM COMPOUNDS

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**PRESERVATIVE BLENDS**  
**CONTAINING QUATERNARY AMMONIUM COMPOUNDS**

This application claims the benefit of U.S. Provisional Application No.  
15 60/273,082, filed March 1, 2001, and U.S. Provisional Application No. 60/345,878, filed  
October 19, 2001, both of which are hereby incorporated by reference.

**Field of the Invention**

This invention relates to antimicrobial compositions containing (a) (i) a  
20 quaternary ammonium compound, (ii) a polymeric quaternary ammonium compound, or (iii)  
a mixture thereof and (b) (i) a cyclic or acyclic ketone acid or salt thereof, (ii) an aromatic  
carboxylic acid or a salt thereof, or (iii) a mixture thereof.

**Background of the Invention**

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Many quaternary ammonium compounds, such as benzethonium chloride, are  
known to be effective as antimicrobial agents and preservatives. However, benzethonium  
chloride and many other quaternary ammonium compounds are expensive. Furthermore, the  
efficacy of quaternary ammonium compounds generally are reduced when incorporated into  
anionic formulations. As a result, there is a continuing need for improved antimicrobial and

preservative compositions which contain low concentrations of quaternary ammonium compounds and maintain their efficacy in anionic formulations.

### Summary of the Invention

5 Applicants have discovered that ketone acids, aromatic carboxylic acids, and salts thereof synergistically enhance the performance of certain quaternary ammonium biocides. The applicants have also discovered that while these quaternary ammonium biocides are frequently inactive in anionic formulations, mixtures containing at least one of these quaternary ammonium biocides and a ketone acid, an aromatic carboxylic acid, salt  
10 thereof, or a mixture thereof are active in anionic formulations.

The present invention provides a composition comprising

- (a) (i) a quaternary ammonium biocide having the formula  $N^+R^1R^2R^3R^4X^-$  where  $R^1$  and  $R^2$  are independently unsubstituted or hydroxy substituted linear or branched  $C_1$ - $C_4$  alkyl,  $-(CH_2CH_2O)_mCH_2CH_2OH$ ,  
15 or  $-(CH_2CH(CH_3)O)_mCH_2CH(CH_3)OH$  where  $m$  is 1 to 10;  $R^3$  is a substituted or unsubstituted benzyl, ethylbenzyl, methylnaphthyl, or linear or branched  $C_1$ - $C_{22}$  alkyl;  $R^4$  is  $-R^5(O)_n(C_6H_5)R^6$  where  $n$  is 0 or 1;  $R^5$  is a substituted or unsubstituted  $C_1$ - $C_8$  alkyl or  $C_1$ - $C_8$  alkoxyalkyl;  $R^6$  is hydrogen or a substituted or unsubstituted, linear or  
20 branched  $C_1$ - $C_{12}$  alkyl; and  $X^-$  is an anion, such as chloride, acetate, borate, propionate, carbonate, bicarbonate, or hydroxide,
- (ii) a polymeric quaternary ammonium biocide, or
- (iii) a mixture thereof; and
- (b) (i) a ketone acid or salt thereof,
- (ii) an aromatic carboxylic acid or a salt thereof, or  
25 (iii) a mixture thereof.

Preferably, the ketone acid is a cyclic ketone acid. The aforementioned mixtures are synergistic.

Another embodiment of the present invention is a method for inhibiting the growth of microorganisms on a substrate by applying an antimicrobial or preserving effective  
5 amount of the composition of the present invention.

### **Detailed Description of the Invention**

Unless otherwise specified, the term "substituted" as used herein includes, but is not limited to, at least one of the following substituents: C<sub>1</sub>-C<sub>12</sub> alkyl (such as a C<sub>1</sub>-C<sub>4</sub> alkyl),  
10 halogen (such as chlorine), nitro, and hydroxy.

The term "biocide" includes, but is not limited to, bactericides, fungicides, pesticides and agents which inhibit the growth of and/or destroy microorganisms and insects.

The term "anionic formulation" as used herein refers to formulations containing one or more anionic compounds, such as anionic surfactants.

15 The ketone acid or aromatic carboxylic acid enhances the biocidal efficacy of the quaternary ammonium biocide. These compositions are useful as antimicrobial, fungicidal, and bactericidal agents and as preservatives in the papermaking, textile, agricultural, and coating industries and in personal care, household, industrial, and institutional products. The composition may be incorporated into substrates susceptible to  
20 microbial growth as a preservative system. For example, the preservative system may be incorporated into or be a personal care product, such as a shampoo, conditioner, cream, lotion, cosmetic, or soap; a household product, such as a fabric softener, laundry detergent, or hard surface cleaner; or an industrial product, such as paint, wood, textile, adhesive, sealant, leather, rope, paper pulp, plastic, fuel, oil, rubber working fluid, metal working fluid, starch,  
25 or mineral slurry, such as a slurry of clay, calcium carbonate, or titanium oxide (TiO<sub>3</sub>).

The applicants have also discovered that while the quaternary ammonium biocides, such as benzethonium chloride, frequently are inactive in anionic formulations, they are active in such formulations in the presence of ketone acids, aromatic carboxylic acids, and salts thereof.

5                   Generally, the preservative system of the present invention acts quickly (e.g., reduces the bacteria count by 95, 99, 99.9, or 99.99% typically within an hour) and maintains efficacy (e.g., maintains less than 10 cfu/g) over long periods of time (e.g., for at least 28 days).

#### 10   Quaternary Ammonium Biocides

According to one preferred embodiment,  $R^5$  is  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$ . More preferably,  $R^4$  is  $[2-[2-(4\text{-diisobutylphenoxy})\text{ethoxy}]\text{ethyl}]$ . According to another preferred embodiment,  $R^4$  is benzyl.

Preferred quaternary ammonium biocides include, but are not limited to, salts  
15 of benzethonium ( $[2-[2-(4\text{-diisobutylphenoxy})\text{ethoxy}]\text{ethyl}]$  dimethylbenzyl ammonium) (also referred to as benzethonium salts), such as benzethonium chloride (available as Hyamine 1622® from Lonza Inc. of Fair Lawn, NJ); and salts of benzalkonium (benzyl alkyl dimethyl ammonium), such as benzalkonium chloride (available as Barquat® MB-50 and Barquat® MB-80 from Lonza Inc. of Fair Lawn, NJ). Preferred benzalkonium salts include, but are not  
20 limited to,  $(\text{C}_{12}\text{-C}_{18})$  alkyl benzyl dimethyl ammonium salts, such as  $(\text{C}_{12}\text{-C}_{18})$  alkyl benzyl dimethyl ammonium chloride.

According to yet another preferred embodiment, the anion  $X^-$  is carbonate.

The quaternary ammonium biocide may optionally be encapsulated by any method known in the art in order to increase its solubility in a desired solvent or formulation.

25 For example, the quaternary ammonium biocide may be encapsulated in cyclodextrin;

calixarenes, such as 4-tert-butylcali[4]arene; liposomes; catezones; or amphiphilic betaine polymers.

#### Polymeric Quaternary Ammonium Biocides

5                    Suitable polymeric quaternary ammonium biocides include, but are not limited to, polymeric quaternary ammonium borates, such as those described in U.S. Patent Nos. 4,970,201 and 5,304,237 (which is hereby incorporated by reference) and poly[oxyethylene(dimethylimino)-ethylene(dimethylimino)] (available as Buckman WSCP from Buckman Laboratories of Memphis, TN).

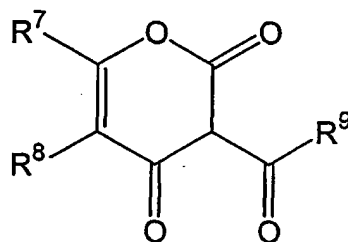
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#### Ketone Acids

The ketone acid may be a cyclic or acyclic ketone acid. The term "cyclic ketone acid" as used herein includes compounds that have a ring containing a carbonyl group.

Suitable cyclic ketone acids include, but are not limited to, those having the

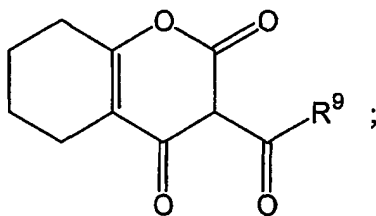
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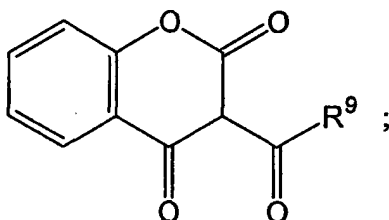
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and salts thereof, wherein  $R^7$ ,  $R^8$ , and  $R^9$  are independently  $C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkenyl,  $C_1$ - $C_{10}$  alkenyl, aryl, aryl substituted with halogen, or  $(C_1$ - $C_{10}$  alkyl)aryl. Preferably,  $R^7$ ,  $R^8$ , and  $R^9$  are independently  $C_1$ - $C_4$  alkyl; or  $R^7$  and  $R^8$  form a 5-12 member ring. Preferred cyclic ketone

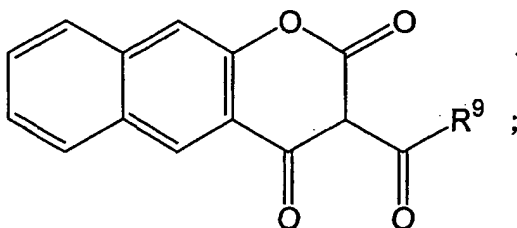
25    acids, include, but are not limited to, those having the formula



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and salts thereof. A more preferred cyclic ketone acid is dehydroacetic acid and salts thereof (including hydrates thereof), such as sodium dehydroacetate (*e.g.*, sodium dehydroacetate hydrate and sodium dehydroacetate monohydrate).

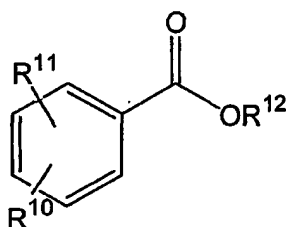
20           The cyclic ketone acid may optionally be encapsulated by any method known in the art to increase its solubility in a desired solvent or formulation. For example, the cyclic ketone acid may be encapsulated in cyclodextrin; calixarenes, such as 4-*tert*-butylcali[4]arene; liposomes; catezones; or amphiphilic betaine polymers. The cyclic ketone acid may be encapsulated by any method known in the art.

A preferred combination of cyclic ketone acid and quaternary ammonium biocide is dehydroacetic acid or a salt thereof and benzethonium chloride. A more preferred combination is sodium dehydroacetate and benzethonium chloride.

## 5 Aromatic Carboxylic Acids

Suitable aromatic carboxylic acids include, but are not limited to, benzoic acids, derivatives thereof, and salts thereof. According to one embodiment, the aromatic carboxylic acid has the formula

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where R<sup>10</sup> and R<sup>11</sup> are independently H, -OH, or -OC(O)CH<sub>3</sub>; and R<sup>12</sup> is H, Na, K, Ca, or Mg.

15 When R<sup>12</sup> is Ca or Mg, the ratio of the aromatic carboxylic acid to Ca or Mg may be 1:1 or 2:1.

For example, the aromatic carboxylic acid can be a hydroxy benzoic acid, derivative thereof, or salt thereof. A preferred hydroxy benzoic acid is salicylic acid and salts thereof. Suitable salts of salicylic acid include, but are not limited to, sodium salicylate.

20 A preferred combination of aromatic carboxylic acid or salt thereof and quaternary ammonium biocide is sodium salicylate and benzethonium chloride.

The composition may include a solvent, such as water and water miscible solvents, including, but not limited to, alcohols, glycols (e.g. glycerin, diglycerin, butylene glycol, butoxydiglycol, propylene glycol, and dipropylene glycol), esters, ethers, polyethers,

25



and any combination of any of the foregoing. For example, the solvent may comprise water and an alcohol, such as phenoxyethanol and/or benzyl alcohol.

Other adjuvants may be included in the composition as known to one of ordinary skill in the art. Suitable adjuvants include, but are not limited to, preservatives; solubilizing agents; chelating agents, such as ethylenediaminetetraacetic acid (EDTA) and salts thereof and zeolites; surfactants, such as cationic, anionic, nonionic, and amphoteric surfactants; antioxidants, such as butylated hydroxyanisole (BHA) and butylhydroxytoluene (BHT); amine oxides; tertiary amines; zinc compounds; hydrotropes; fluoride compounds; magnesium salts; calcium salts; carboxylic acids; phosphates; phosphonates; formaldehyde donors; glycereth-7; myristyl myristate; glutaraldehydes; biguanides; natural products, such as geraniol, usnic acid, and tea tree oils; and any combination of any of the foregoing.

Suitable preservatives include, but are not limited to, quaternary ammonium chlorides; quaternary ammonium carbonates; benzalkonium chloride; iodine containing compounds, such as 3-iodo-2-propynyl butyl carbamate (IPBC); hydantoins, such as dimethylhydantoin and halogenated hydantoins; isothiazolinones; parabens, such as methylparaben, ethylparaben, and propylparaben; chloroxylenol; chlorhexidine; phenoxyethanol; benzyl alcohol; phenethyl alcohol; benzoic acid and salts thereof; chlorobutanol; sorbic acid and salts thereof; triclosan; triclocarban; and any combination of any of the foregoing.

Typically, the composition is an aqueous or oil based system and is not an emulsion. In oil based systems, the quaternary ammonium biocide is preferably not encapsulated and the ketone acid is preferably not a hydrate. A suitable solvent for an oil based system is phenoxyethanol and/or benzyl alcohol.

The composition can be a liquid or a solid.

The weight ratio of (1) ketone acid, aromatic carboxylic acid, salts thereof, or mixtures thereof to (2) quaternary ammonium biocide, polymeric quaternary ammonium

biocide, or mixtures thereof broadly ranges from about 0.00056:1 to about 1990:1 and preferably ranges from about 0.0056:1 to about 1400:1.

To prepare a formulation containing the composition of the present invention, a concentrate is generally first prepared. Table A illustrates the components and the ranges of components present in a typical concentrate (based upon 100% total weight of concentrate).

Table A

Ranges	Quaternary Ammonium Biocide, Polymeric Quaternary Ammonium Biocide, or Mixtures Thereof	Ketone Acid, Aromatic Carboxylic Acid, Salts Thereof, or Mixtures Thereof
Broad	from about 0.05 to about 90%	from about 0.05 to about 99.5%
Preferred	from about 0.5 to about 40%	from about 0.50 to about 70%
More Preferred	from about 1 to about 20%	from about 5 to about 40%

Before use, the concentrate is diluted, preferably with the same solvent as was used in the concentrate. Use dilutions of the composition typically comprise a biocidally, fungicidally, or bactericidally effective amount of (1) the quaternary ammonium biocide and/or polymeric quaternary ammonium biocide (i.e., component (a)) and/or (2) the mixture of components (a) and (b) (where component (b) is the ketone acid, aromatic carboxylic acid or salt thereof, or a mixture thereof). The use dilutions also typically comprise a biocidal, fungicidal, or bactericidal enhancing (or potentiating) effective amount of the ketone acid or salt thereof, aromatic carboxylic acid or salt thereof, or mixture thereof (i.e., component (b)). Generally, use dilutions contain from about 0.0001% or 0.01% to about 2% by weight of the concentrate. According to one preferred embodiment, use dilutions contain from about 0.1 to about 1% by weight of the concentrate. Table B illustrates the components and generally

the ranges of components present in the use dilution (based upon 100% total weight of use dilution).

Table B

5	Ranges	Quaternary Ammonium Biocide, Polymeric Quaternary Ammonium Biocide, or Mixtures Thereof	Ketone Acid, Aromatic Carboxylic Acid, Salts Thereof, or Mixtures Thereof
	Broad	from about 0.00005 to about 0.45%	from about 0.00005 to about 0.5%
	Preferred	from about 0.0005 to about 0.2%	from about 0.0005 to about 0.35%
10	More Preferred	from about 0.001 to about 0.1%	from about 0.005 to about 0.2%

Yet another preferred embodiment is a preservative formulation comprising dehydroacetic acid, benzethonium chloride, salicylic acid and, optionally, benzoic acid, phenoxyethanol, and benzyl alcohol. The formulation in concentrated form may contain from about 5 to about 40% by weight of dehydroacetic acid, from about 1 to about 20% by weight of benzethonium chloride, from about 2.5 to about 20% by weight of salicylic acid, and, optionally, from about 2.5 to about 20% by weight of benzoic acid, from about 20 to about 50% by weight of phenoxyethanol, and from about 5 to about 50% by weight of benzyl alcohol, based upon 100% total weight of preservative formulation. A more preferred embodiment of the preservative formulation contains about 10% by weight of dehydroacetic acid, about 5% by weight of benzethonium chloride, and about 10% by weight of salicylic acid, and, optionally, about 10% by weight of benzoic acid, about 35% by weight of phenoxyethanol, and about 30% by weight of benzyl alcohol, based upon 100% total weight of preservative formulation.

Another embodiment of the present invention is a method for inhibiting the growth of microorganisms, bacteria (e.g., *S. aureus* (ATCC # 6538), *P. aeruginosa* (ATCC

# 9027), and *E. coli* (ATCC # 8739)), and/or fungi (e.g., *Candida albicans* and *Aspergillus niger*) on a substrate by applying an antimicrobial, bactericidal, or fungicidal effective amount of the composition of the present invention to the substrate. The composition may be applied to the substrate by any method known in the art including, but not limited to, brushing, dipping, soaking, vacuum impregnation, and pressure treatment.

The composition of the present invention may be prepared by mixing the ketone acid or salt thereof, the aromatic carboxylic acid or salt thereof, quaternary ammonium biocide, polymeric quaternary ammonium biocide, solvents, and adjuvants. The mixture may be heated and/or stirred to expedite mixing.

#### **Description of the Preferred Embodiments**

The following examples illustrate the invention without limitation. All parts and percentages are given by weight unless otherwise indicated.

##### **Example 1**

Each anionic shampoo sample in Table 1 below was tested as follows. A standardized mixed bacterial solution was prepared according to the following procedure. 3 agar stabs of *S. aureus* (ATCC # 6538), *P. aeruginosa* (ATCC # 9027), and *E. coli* (ATCC # 8739) were separately incubated at about 35°C for about 24 hours. Each stab was then washed with 3 mL of sterile 0.85% saline solution. The washes of the 3 stabs were pooled together to form an organism mixture. The absorbance of the organism mixture at 530 nm was adjusted to about 1.00 by adding saline. The spectrometer was calibrated with a saline blank. A 5 mL aliquot of the organism mixture was mixed together to produce the standardized mixed bacterial solution. Then, 40 g of each shampoo sample was inoculated with 0.2 mL of the standardized mixed bacterial solution and mixed. 1 g of the mixture was added to a sterile 20 x 150 mm screw cap test tube.

9 mL of sterile D/E neutralizer broth was added to the test tube and mixed to form a  $10^{-1}$  dilution, . Serial dilutions were prepared through to a  $10^{-6}$  dilution with phosphate buffered water. The serial dilutions were plated onto Tryptic Soy Agar and incubated for 2 days at about 35°C. Bacteria counts were performed after 0 and 14 days. The results are shown in Table 1.

The anionic protein shampoo composition was comprised of 35% by weight of sodium lauryl ether sulfate; 25% by weight of triethanolamine lauryl sulfate; 3% by weight coconut diethanolamide (cocamide DEA); 1% by weight of hydrolyzed collagen, available as Polypro 5000™ from Hormel Foods of Austin, MN; and 36% by weight of deionized water.

The sodium dehydroacetate monohydrate, sodium salicylate, and Hyamine® 1622 shampoo samples were prepared by mixing the appropriate amounts of the preservatives and the aforementioned anionic protein shampoo composition and heating the mixture to about 50° C for about 15 minutes.

Table 1

Shampoo	<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>E. coli</i> (cfu/g)	
	Day 0	Day 14
Unpreserved Anionic Protein Shampoo Composition	$3.0 \times 10^6$	$3.0 \times 10^7$
0.25% Sodium Dehydroacetate Monohydrate <sup>1</sup> and 0.50% Hyamine <sup>®</sup> 1622 <sup>2</sup> *	$3.0 \times 10^6$	< 10
0.5% Sodium Salicylate <sup>3</sup> and 0.5% Hyamine <sup>®</sup> 1622 <sup>2</sup> *	$3.0 \times 10^6$	< 10
0.5% Sodium Dehydroacetate Monohydrate <sup>1</sup> *	$3.0 \times 10^6$	$4.0 \times 10^3$
1.0% Hyamine <sup>®</sup> 1622 <sup>2</sup> *	$3.0 \times 10^6$	$8.5 \times 10^6$
1.0% Sodium Salicylate <sup>3</sup> *	$3.0 \times 10^6$	$5.0 \times 10^2$

All percentages in Table 1 are in percent by weight based upon 100% by weight of total shampoo.

<sup>1</sup> Sodium dehydroacetate monohydrate is available from Lonza Inc. of Fair Lawn, NJ.

<sup>2</sup> Hyamine<sup>®</sup> 1622 is diisobutylphenoxyethoxyethyl dimethylbenzyl ammonium chloride (benzethonium chloride) and is available from Lonza Inc. of Fair Lawn, NJ.

<sup>3</sup> Sodium salicylate is available from Sigma Chemical Co. of St. Louis, MO.

\* - Below the specified concentrations of preservative, the shampoos contained  $\geq 10$  cfu/g after 14 days.

Synergism for the sodium dehydroacetate monohydrate/Hyamine<sup>®</sup> 1622 and sodium salicylate/Hyamine<sup>®</sup> 1622 solutions in Table 1 against *S. aureus*, *P. aeruginosa*, and *E. coli* was calculated by the method described in C.E. Kull *et al.*, "Mixtures of Quaternary

Ammonium Compounds and Long-chain Fatty Acids as Antifungal Agents", *Applied Microbiology*, 9:538-541 (1961). The synergism value ( $Q_A/Q_a + Q_B/Q_b$ ) in Table 2 was determined.  $Q_A$  is the concentration of sodium dehydroacetate monohydrate or sodium salicylate (in percent by weight) in the mixture, which yielded 100% retardation of the bacteria, *i.e.*, resulted in a plate count of  $< 10$  cfu/g after 14 days.  $Q_a$  is the concentration of sodium dehydroacetate monohydrate or sodium salicylate alone (in percent by weight) required to yield 100% retardation of the bacteria.  $Q_B$  is the concentration of Hyamine® 1622 (in percent by weight) in the mixture, which yielded 100% retardation of the bacteria.  $Q_b$  is the concentration of Hyamine® 1622 alone (in percent by weight) required to yield 100% retardation of the bacteria.

When the value of ( $Q_A/Q_a + Q_B/Q_b$ ) is less than one, the mixture is synergistic. Values for ( $Q_A/Q_a + Q_B/Q_b$ ) of 1 and greater than 1, represent an additive effect and an antagonistic effect, respectively.

The results are shown in Table 2 below.

Table 2

Preservative Mixture	$Q_A$	$Q_B$	$Q_a$	$Q_b$	$Q_A/Q_a + Q_B/Q_b$
0.25% Sodium Dehydroacetate Monohydrate and 0.50% Hyamine® 1622	0.25%	0.50%	$>0.50\%$	$>1.00\%$	$< 1$
0.5% Sodium Salicylate and 0.5% Hyamine® 1622	0.5%	0.5%	$>1.00\%$	$>1.00\%$	$< 1$

Example 2

The procedure described in Example 1 was repeated with the anionic shampoos in Table 3 below. The bacterial counts were performed after 0 and 7 days. The dehydroacetic acid (available from Lonza Inc. of Fair Lawn, N.J.) and Hyamine® 1622 shampoo samples were prepared by mixing the appropriate amounts of the preservatives and the anionic protein shampoo composition and heating the mixture to about 50°C for about 15 minutes. The results are shown in Table 3 below.

Table 3

Shampoo	<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>E. Coli</i> (cfu/g)	
	Day 0	Day 7
Unpreserved Anionic Protein Shampoo Composition	$3.0 \times 10^6$	$3.0 \times 10^7$
0.1% Dehydroacetic Acid and 0.5% Hyamine® 1622	$3.0 \times 10^6$	<10
0.2% Dehydroacetic Acid	$2.5 \times 10^6$	$4.4 \times 10^4$
1.0% Hyamine® 1622	$3.0 \times 10^6$	$3.0 \times 10^7$

Synergism for the dehydroacetic acid/Hyamine® 1622 mixture in Table 3 against *S. aureus*, *P. aeruginosa*, and *E. coli* was determined by the procedure described in Example 1. The results are shown in Table 4 below.



Table 4

Preservative Mixture	$Q_A$	$Q_a$	$Q_B$	$Q_b$	$Q_A/Q_a + Q_B/Q_b$
0.1% Dehydroacetic Acid and 0.5% Hyamine® 1622	0.1%	> 0.2%	0.5%	>1.0%	<1

Example 3

The procedure described in Example 1 was repeated with the anionic shampoos in Table 5 below. The salicylic acid (available from Spectrum Chemical of New Brunswick, N.J.) and Hyamine® 1622 shampoo samples were prepared by mixing the appropriate amounts of the preservatives and the anionic protein shampoo composition and heating the mixture to about 50°C for 15 minutes. The results are shown in Table 5 below.

Table 5

Shampoo	<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>E. coli</i> (cfu/g)	
	Day 0	Day 14
Unpreserved Anionic Protein Shampoo Composition	$3.0 \times 10^6$	$1.0 \times 10^7$
0.1% Salicylic Acid and 0.5% Hyamine® 1622	$3.0 \times 10^6$	<10
1.0% Hyamine® 1622	$3.0 \times 10^6$	$8.5 \times 10^6$
0.2% Salicylic Acid	$3.1 \times 10^6$	$6.5 \times 10^6$

Synergism for the salicylic acid/Hyaminate® 1622 solution in Table 5 against *S. aureus*, *P. aeruginosa*, and *E. coli* was determined by the procedure described in Example 1. The results are shown in Table 6 below.

Table 6

Preservative Mixture	$Q_A$	$Q_a$	$Q_B$	$Q_b$	$Q_A/Q_a + Q_B/Q_b$
0.1% Salicylic Acid and 0.5% Hyaminate®	0.1%	> 0.2%	0.5%	>1.0%	<1

Example 4

A preservative formulation as described in Table 7 below was prepared by mixing the ingredients.

Table 7

Ingredient	% (w/w)
Dehydroacetic Acid	10
Salicylic Acid	10
Benzoic Acid	10
Benzethonium Chloride	1
Phenoxyethanol	37
Benzyl Alcohol	32

Example 5

A preservative formulation as described in Table 8 below was prepared by mixing the ingredients.

Table 8

Ingredient	% (w/w)
Dehydroacetic Acid	10
Salicylic Acid	10
Benzoic Acid	10
Benzethonium Chloride	5
Phenoxyethanol	35
Benzyl Alcohol	30

Example 6

Each anionic shampoo sample in Table 9 below was tested as follows. A standard mixed bacterial solution was prepared according to the following procedure. 2 agar slants of *Candida albicans* and 4 agar slants of *Aspergillus niger* were separately incubated at about 25°C for about 48 hours and 7 days, respectively. Each slant was washed with 3 mL of sterile 0.85% saline solution, collected and macerated in a tissue grinder. Sufficient amounts of 0.85% saline solution were added to each slant to obtain a visual count under a microscope with a Neubauer Hemocytometer of each inoculum of *C. albicans* and *A. niger*. Equal volumes of each standardized inoculum of *C. albicans* and *A. niger* were mixed together to form the standardized mixed fungal solution.

40g of each shampoo sample was inoculated with 0.4 mL of the standardized mixed fungal solution and mixed. 1g of the mixture was added to a sterile 20 x 150mm screw cap test tube.

9mL of sterile D/E neutralizer broth was added to the test tube and mixed to form a  $10^{-1}$  dilution. Serial dilutions were prepared through to a  $10^{-6}$  dilution with phosphate buffered water. The serial dilutions were plated onto Sabourand dextrose agar and incubated 5 days at about 25°C. Fungal counts were performed after 0 and 14 days. The results are shown in Table 9.

The anionic protein shampoo composition is described in Example 1. The shampoo samples were prepared by mixing the appropriate amounts of the preservatives and the anionic protein shampoo composition and heating the mixture to about 50°C for about 15 minutes.

Table 9

Shampoo	Fungal Plate Count (cfu/g)	
	Day 0	Day 14
Unpreserved Anionic Protein Shampoo Composition	$1.6 \times 10^4$	$1.5 \times 10^5$
1.0% Benzethonium Chloride	$2.4 \times 10^5$	$2.0 \times 10^4$
0.6% Example 4	$2.7 \times 10^5$	$1.0 \times 10^3$
0.6% Example 5	$1.1 \times 10^5$	$7.0 \times 10^1$

The results in Table 9 show that benzethonium chloride is inactivated in anionic formulations. 1.0% or 10,000 ppm of benzethonium chloride is ineffective at reducing the mixed fungi in the anionic shampoo. Shampoo sample containing 0.6% of Example 4 (60 ppm of benzethonium chloride) exhibited a 2 log reduction in the fungal plate count. The shampoo sample containing 0.6% of Example 5 (300 ppm of benzethonium chloride) exhibited a 4 log reduction in the fungal plate count. This demonstrates that the preservative blend of the present invention potentiates the fungicidal efficacy of the benzethonium chloride in anionic formulations.

#### Example 7

Each cream sample in Table 10 below was tested by the procedure described in Example 1. A glyceryl monostearate (GMS) cream as described in Table 10 below was prepared as follows. The polyoxyethylene glyceryl monostearate, glyceryl

monostearate, cetearyl alcohol, and myristyl propionate were mixed and heated to 60° C in a first container. The glycerin and sterile deionized water were mixed and heated to 60° C in a second container. The solution in the first container was poured into the second container. The second container was maintained at 60° C for 10 minutes. The solution in the second container was allowed to cool. The pH of the solution was adjusted to pH 7 with sodium hydroxide to yield the GMS cream.

Table 10

Ingredient Trade Name	Chemical Name	Amount (% w/w)
Aldospense® MS-20 (Lonza)	Polyoxyethylene (POE) glyceryl monostearate	4.00
Aldo® (Lonza)	Glyceryl monostearate	6.00
TA 1618 (Proctor & Gamble)	Cetearyl alcohol	1.50
Lonzest® 143-S (Lonza)	Myristyl propionate	8.00
Glycon® G-100 (Lonza)	Glycerin	5.00
-	Sterile Deionized Water	75.50
Total		100.00

The 0.4% Example 5 sample was prepared by mixing the appropriate amounts of the preservatives and the GMS cream and heating the mixture to 50° C for 10-15 minutes.

The results are shown in Table 11 below.

Table 11

Cream	<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>E. coli</i> (cfu/g)			
	1 Hour	3 Hours	24 Hours	28 Days
Unpreserved GMS Cream	$5.3 \times 10^6$	$6.3 \times 10^6$	$5.0 \times 10^6$	$3.0 \times 10^6$
0.4% Example 5	<10	<10	<10	<10

While most preservatives have slow efficacy (e.g., require 3 or more days to reduce the number of microorganisms), the preservative system shown in Table 11 acts quickly (e.g., typically within an hour) and maintains efficacy over long periods of time (e.g., for at least 28 days).

All patents, applications, articles, publications, and test methods mentioned above are hereby incorporated by reference.

Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. Such obvious variations are within the full intended scope of the appended claims.

**IN THE CLAIMS:**

- 1           1.     A composition comprising:
- 2                   (a)   (i)    a quaternary ammonium biocide having the formula
- 3                                $N^+R^1R^2R^3R^4 X^-$ ,
- 4                               (ii)   a polymeric quaternary ammonium biocide, or
- 5                               (iii)   a mixture thereof; and
- 6                   (b)   (i)    a ketone acid or salt thereof,
- 7                               (ii)   an aromatic carboxylic acid or a salt thereof, or
- 8                               (iii)   a mixture thereof,
- 9     wherein  $R^1$  and  $R^2$  are independently unsubstituted or hydroxy substituted linear or
- 10    branched  $C_1-C_4$  alkyl,  $-(CH_2CH_2O)_mCH_2CH_2OH$ , or  $-(CH_2CHCH_3O)_mCH_2CHCH_3OH$
- 11    where  $m$  is 1 to 10;  $R^3$  is a substituted or unsubstituted benzyl, ethylbenzyl,
- 12    methylnaphthyl, or linear or branched  $C_1-C_{22}$  alkyl;  $R^4$  is  $-R^5(O)_n(C_6H_5)R^6$  where  $n$  is 0 or
- 13    1;  $R^5$  is a substituted or unsubstituted  $C_1-C_8$  alkyl or  $C_1-C_8$  alkoxyalkyl;  $R^6$  is hydrogen or
- 14    a substituted or unsubstituted, linear or branched  $C_1-C_{12}$  alkyl; and  $X^-$  is an anion.

- 1           2.     The composition of claim 1, wherein  $R^5$  is  $-CH_2CH_2OCH_2CH_2-$ .

- 1           3.     The composition of claim 2, wherein  $R^4$  is [2-[2-(4-diisobutyl-
- 2    phenoxy)ethoxy]ethyl].

- 1           4.     The composition of claim 1, wherein the quaternary ammonium biocide is a
- 2    salt of benzethonium.

1           5.     The composition of claim 4, wherein the quaternary ammonium biocide is  
2     benzethonium chloride.

1           6.     The composition of claim 1, wherein R<sup>4</sup> is benzyl.

1           7.     The composition of claim 1, wherein the quaternary ammonium biocide is a  
2     salt of benzalkonium.

1           8.     The composition of claim 7, wherein the quaternary ammonium biocide is  
2     benzalkonium chloride.

1           9.     The composition of claim 7, wherein the quaternary ammonium biocide is a  
2     salt of (C<sub>12</sub>-C<sub>18</sub>) alkyl benzyl dimethyl ammonium.

1           10.    The composition of claim 9, wherein the quaternary ammonium biocide is  
2     (C<sub>12</sub>-C<sub>18</sub>) alkyl benzyl dimethyl ammonium chloride.

1           11.    The composition of claim 1, wherein X<sup>-</sup> is chloride or carbonate.

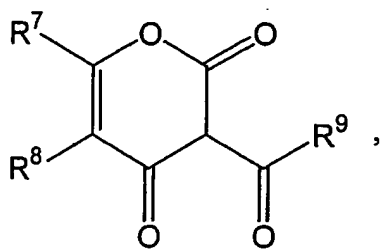
1           12.    The composition of claim 11, wherein X<sup>-</sup> is chloride.

1           13.    The composition of claim 11, wherein X<sup>-</sup> is carbonate.

1           14.    The composition of claim 1, wherein the ketone acid is a cyclic ketone acid  
2     or a salt thereof.



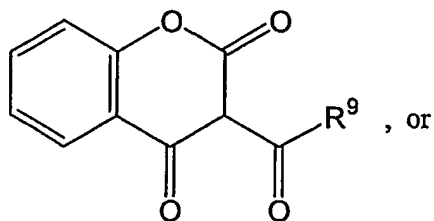
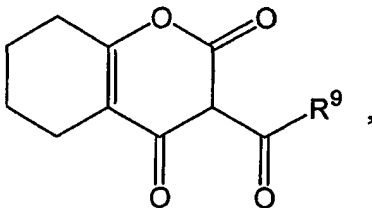
1           15.    The composition of claim 14, wherein the cyclic ketone acid has the  
2    formula

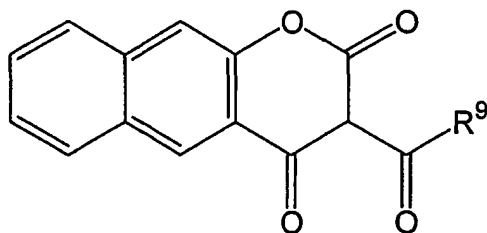


8           wherein R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are independently C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkenyl, C<sub>1</sub>-C<sub>10</sub> alkenyl, aryl,  
9    aryl substituted with halogen, or (C<sub>1</sub>-C<sub>10</sub> alkyl)aryl.

1           16.    The composition of claim 15, wherein R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are independently C<sub>1</sub>-  
2    C<sub>4</sub> alkyl; or R<sup>7</sup> and R<sup>8</sup> form a 5-12 member ring.

1           17.    The composition of claim 15, wherein the cyclic ketone acid has the  
2    formula





18. The composition of claim 14, wherein the ketone acid is dehydroacetic acid or a salt thereof.

19. The composition of claim 1, wherein the ketone acid is sodium dehydroacetate.

20. The composition of claim 1, wherein the ketone acid is encapsulated.

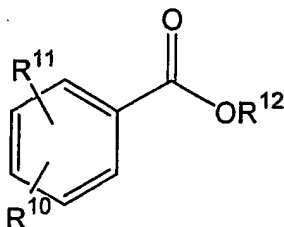
21. The composition of claim 18, wherein the dehydroacetic acid or salt thereof is encapsulated in cyclodextrin.

22. The composition of claim 1, wherein the quaternary ammonium biocide is benzethonium chloride and the ketone acid is dehydroacetic acid or a salt thereof.

23. The composition of claim 1, wherein the quaternary ammonium biocide is benzalkonium chloride and the ketone acid is dehydroacetic acid or a salt thereof.

24. The composition of claim 1, wherein the aromatic carboxylic acid is benzoic acid, derivative thereof, or salt thereof.

1           25.    The composition of claim 1, wherein the aromatic carboxylic acid has the  
2    formula



3  
4  
5  
6  
7    wherein R<sup>10</sup> and R<sup>11</sup> are independently H, -OH, or -OC(O)CH<sub>3</sub>; and R<sup>12</sup> is H, Na, K, Ca, or  
8    Mg.

1           26.    The composition of claim 1, wherein the aromatic carboxylic acid is a  
2    hydroxy benzoic acid, derivative thereof, or salt thereof.

1           27.    The composition of claim 26, wherein the hydroxy benzoic acid is salicylic  
2    acid or a salt thereof.

1           28.    The composition of claim 27, wherein the salt of salicylic acid is sodium  
2    salicylate.

1           29.    The composition of claim 1, wherein the quaternary ammonium biocide is  
2    benzethonium chloride and the aromatic carboxylic acid is sodium salicylate.

1           30.    The composition of claim 1, wherein the quaternary ammonium biocide is  
2    benzalkonium chloride and the aromatic carboxylic acid is sodium salicylate.

1           31.    The composition of claim 1, further comprising a solvent.

1           32.    The composition of claim 31, wherein the solvent is water, an alcohol, a  
2           glycol, an ester, an ether, a polyether or any combination of any of the foregoing.

1           33.    The composition of claim 1, wherein the composition comprises a  
2           biocidally effective amount of the quaternary ammonium biocide.

1           34.    The composition of claim 1, wherein the composition comprises a  
2           fungicidally effective amount of the quaternary ammonium biocide.

1           35.    The composition of claim 1, wherein the weight ratio of the ketone acid to  
2           the quaternary ammonium biocide ranges from about 0.00056:1 to about 1990:1.

1           36.    The composition of claim 35, wherein the weight ratio of the ketone acid to  
2           the quaternary ammonium biocide ranges from about 0.0056:1 to about 1400:1.

1           37.    The composition of claim 1, wherein said composition comprises from  
2           about 0.00005 to about 0.5% by weight of ketone acid and from about 0.00005 to about  
3           0.45% by weight of quaternary ammonium biocide, based upon 100% weight of total  
4           composition.

1           38.    The composition of claim 37, wherein said composition comprises from  
2           about 0.0005 to about 0.35% by weight of ketone acid and from about 0.0005 to about  
3           0.2% by weight of quaternary ammonium biocide, based upon 100% weight of total  
4           composition.

1           39.    The composition of claim 1, wherein the weight ratio of the aromatic  
2    carboxylic acid to the quaternary ammonium biocide ranges from about 0.00056:1 to about  
3    1990:1.

1           40.    The composition of claim 39, wherein the weight ratio of the aromatic  
2    carboxylic acid to the quaternary ammonium biocide ranges from about 0.0056:1 to about  
3    1400:1.

1           41.    The composition of claim 1, wherein said composition comprises from  
2    about 0.00005 to about 0.5% by weight of aromatic carboxylic acid and from about  
3    0.00005 to about 0.45% by weight of quaternary ammonium biocide, based upon 100%  
4    weight of total composition.

1           42.    The composition of claim 41, wherein said composition comprises from  
2    about 0.0005 to about 0.35% by weight of aromatic carboxylic acid and from about 0.0005  
3    to about 0.2% by weight of quaternary ammonium biocide, based upon 100% weight of  
4    total composition.

1           43.    An antimicrobial composition comprising a synergistic mixture of:

2           (a)    dehydroacetic acid or a salt thereof; and

3           (b)    benzethonium chloride.

1           44.    An antimicrobial composition comprising a synergistic mixture of:

2           (a)    salicylic acid or a salt thereof; and

3           (b)    benzethonium chloride.

1           45.    A method of inhibiting the growth of microorganisms comprising applying  
2           an effective amount of the composition of claim 1.

1           46.    A preservative formulation comprising a synergistic mixture of:  
2           (a)    dehydroacetic acid or a salt thereof;  
3           (b)    a benzethonium salt; and  
4           (c)    salicylic acid or a salt thereof.

1           47.    The preservative formulation of claim 46, further comprising:  
2           (d)    benzoic acid or a salt thereof;  
3           (e)    phenoxyethanol; and  
4           (f)    benzyl alcohol.

1           48.    The preservative formulation of claim 47 comprising:  
2           (a)    from about 5 to about 40% by weight of dehydroacetic acid;  
3           (b)    from about 1 to about 20% by weight of benzethonium chloride;  
4           (c)    from about 2.5 to about 20% by weight of salicylic acid;  
5           (d)    from about 2.5 to about 20% by weight of benzoic acid;  
6           (e)    from about 20 to about 50% by weight of phenoxyethanol; and  
7           (f)    from about 5 to about 50% by weight of benzyl alcohol,  
8           based upon 100% total weight of preservative formulation.

1           49.    The preservative formulation of claim 48 comprising:  
2           (a)    about 10% by weight of dehydroacetic acid;  
3           (b)    about 5% by weight of benzethonium chloride;  
4           (c)    about 10% by weight of salicylic acid;

- 5           (d)    about 10% by weight of benzoic acid;  
6           (e)    about 35% by weight of phenoxyethanol; and  
7           (f)    about 30% by weight of benzyl alcohol,  
8    based upon 100% total weight of preservative formulation.

1           50.    A composition comprising from about 0.01 to about 2% by weight of the  
2    preservative composition of claim 48.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JS 02/06305

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A01N39/00 A01N33/12 //(A01N39/00,43:16,37:40,37:10),  
(A01N33/12,43:16,37:40,37:10)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 5204 (C-085), 24 December 1981 (1981-12-24) & JP 56 123906 A (NIPPON SYNTHETIC CHEM IND), 29 September 1981 (1981-09-29)	1,6-19, 23, 31-38,45
Y	abstract --- -/--	1-50

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

3 July 2002

Date of mailing of the international search report

17/07/2002

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/06305

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 198220  Derwent Publications Ltd., London, GB;  Class D21, AN 1982-40141E  XP002204396  &amp; JP 57 058624 A (NIPPON SYNTHETIC CHEM  IND CO), 8 April 1982 (1982-04-08)  abstract  -&amp; PATENT ABSTRACTS OF JAPAN  vol. 6131 (C-114),  17 July 1982 (1982-07-17)  &amp; JP 57 058624 A  abstract</p>	1,6-19, 23, 31-38,45
X	<p>DATABASE WPI  Section Ch, Week 198220  Derwent Publications Ltd., London, GB;  Class B05, AN 1982-40142E  XP002204397  &amp; JP 57 058625 A (NIPPON SYNTHETIC CHEM  IND CO), 8 April 1982 (1982-04-08)  abstract  -&amp; PATENT ABSTRACTS OF JAPAN  vol. 6131 (C-114),  17 July 1982 (1982-07-17)  &amp; JP 57 058625 A  abstract</p>	1,6-19, 23, 31-38,45
X	<p>DATABASE WPI  Section Ch, Week 197824  Derwent Publications Ltd., London, GB;  Class A60, AN 1978-43131A  XP002204398  &amp; JP 53 050245 A (NIPPON SYNTHETIC CHEM  IND CO), 8 May 1978 (1978-05-08)  abstract  -&amp; PATENT ABSTRACTS OF JAPAN  vol. 2089 (C-018),  21 July 1978 (1978-07-21)  &amp; JP 53 050245 A  abstract</p>	1,6-19, 23, 31-38,45
X	<p>DATABASE WPI  Section Ch, Week 199624  Derwent Publications Ltd., London, GB;  Class A60, AN 1996-235901  XP002204399  &amp; JP 08 092013 A (SHINTO TORYO KK),  9 April 1996 (1996-04-09)  abstract</p>	1,6-13, 24-26, 31-34, 39-42,45
Y	abstract	1-50

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## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 02/06305

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 07331 A (HOLLENBERG DETLEF ;HENKEL KGAA (DE); SEIDEL KURT (DE); PRIEBE CHRI) 18 February 1999 (1999-02-18)  page 1, paragraph 1 page 1, paragraph 4 -page 3, paragraph 2 page 6, paragraph 4 -page 7, paragraph 4	1,6-13, 24-28, 30-36, 39-42,45
Y	-----	1-50
Y	DATABASE WPI Section Ch, Week 199706 Derwent Publications Ltd., London, GB; Class B05, AN 1997-061702 XP002204400 & JP 08 310925 A (ARIMINO KK), 26 November 1996 (1996-11-26) abstract	20,21
X	DE 33 08 303 A (KYMIN OY KYMMENE AB) 29 September 1983 (1983-09-29)  claims 1,3,5 page 5, paragraph 3 page 6, paragraph 2 page 7, paragraph 1	1,6-13, 24-26, 31-34, 39-42,45
X	DE 20 45 337 A (H.GOOD) 1 April 1971 (1971-04-01)  page 1, paragraph 1 page 1, paragraph 3 -page 2, paragraph 1 page 3, line 20 - line 23 page 4, paragraph 1 page 5, paragraph 1	1,7-13, 24-28, 31-34, 39-42
X	EP 0 265 202 A (UNILEVER PLC ;UNILEVER NV (NL)) 27 April 1988 (1988-04-27)  page 2, line 29 - line 56 page 3, line 19 - line 23  ----- -/-	1,7-13, 24-28, 31-34, 39-42

## INTERNATIONAL SEARCH REPORT

Inter      nal Application No

PCT/US 02/06305

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 200055  Derwent Publications Ltd., London, GB;  Class B05, AN 2000-582016  XP002204401  &amp; JP 2000 212090 A (ITO M),  2 August 2000 (2000-08-02)  abstract  -&amp; PATENT ABSTRACTS OF JAPAN  vol. 2000, no. 11,  3 January 2001 (2001-01-03)  &amp; JP 2000 212090 A  abstract</p> <p>---</p>	1-13, 24-34, 39-42, 44,45
X	<p>DATABASE WPI  Section Ch, Week 197450  Derwent Publications Ltd., London, GB;  Class D16, AN 1974-86415V  XP002204402  &amp; JP 49 042901 B (S MINO),  18 November 1974 (1974-11-18)  abstract</p> <p>---</p>	1,6-19, 23, 31-38,45
X	<p>DATABASE WPI  Section Ch, Week 199340  Derwent Publications Ltd., London, GB;  Class A96, AN 1993-317351  XP002204403  &amp; JP 05 229904 A (TAKAHASHI T),  7 September 1993 (1993-09-07)  abstract  -&amp; PATENT ABSTRACTS OF JAPAN  vol. 0176, no. 89 (C-1143),  16 December 1993 (1993-12-16)  &amp; JP 05 229904 A  abstract</p> <p>---</p>	1,6-13, 24-26, 31-34, 39-42,45
Y	<p>US 5 885 593 A (EPSTEIN HOWARD)  23 March 1999 (1999-03-23)  the whole document</p> <p>---</p>	20,21
P,X	<p>DATABASE WPI  Section Ch, Week 200164  Derwent Publications Ltd., London, GB;  Class D21, AN 2001-567597  XP002204404  &amp; JP 2001 139993 A (FUMAKILA KK),  22 May 2001 (2001-05-22)  abstract</p> <p>---</p>	1-50
A	<p>WO 94 27436 A (DECICCO BENEDICT T ;KEEVEN  JAMES KEVIN (US))  8 December 1994 (1994-12-08)  page 3, line 21 -page 4, line 20</p> <p>---</p> <p style="text-align: center;">-/--</p>	1-50

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/06305

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 40 26 756 A (TURNER GMBH) 27 February 1992 (1992-02-27) page 2, line 16 - line 36 -----	1-50
A	EP 0 339 121 A (STERLING DRUG INC) 2 November 1989 (1989-11-02) page 2, line 52 -page 5, line 8 -----	1-50

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/06305

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 56123906	A	29-09-1981	NONE	
JP 57058624	A	08-04-1982	NONE	
JP 57058625	A	08-04-1982	NONE	
JP 53050245	A	08-05-1978	JP 960456 C JP 53042780 B	28-06-1979 14-11-1978
JP 8092013	A	09-04-1996	NONE	
WO 9907331	A	18-02-1999	DE 19733684 A1 AU 8733198 A BR 9811843 A CN 1268047 T WO 9907331 A1 EP 0993298 A1 HU 0100333 A2 JP 2001513488 T PL 338475 A1 SK 1492000 A3 TR 200000270 T2	11-02-1999 01-03-1999 08-08-2000 27-09-2000 18-02-1999 19-04-2000 28-06-2001 04-09-2001 06-11-2000 11-07-2000 21-09-2000
JP 8310925	A	26-11-1996	NONE	
DE 3308303	A	29-09-1983	FI 63513 B FI 830374 A ,B, CA 1196452 A1 DE 3308303 A1 FR 2523404 A1 NO 830895 A ,B, SE 459795 B SE 8301444 A US 4585795 A	31-03-1983 20-09-1983 12-11-1985 29-09-1983 23-09-1983 20-09-1983 07-08-1989 20-09-1983 29-04-1986
DE 2045337	A	01-04-1971	CH 548777 A AT 304770 B DE 2045337 A1 FR 2061766 A5 GB 1301316 A IT 1001464 B	15-05-1974 15-12-1972 01-04-1971 25-06-1971 29-12-1972 20-04-1976
EP 0265202	A	27-04-1988	AU 596875 B2 AU 7978587 A CA 1287796 A1 EP 0265202 A2 NZ 222149 A US 5000867 A ZA 8707871 A	17-05-1990 21-04-1988 20-08-1991 27-04-1988 27-10-1989 19-03-1991 28-06-1989
JP 2000212090	A	02-08-2000	NONE	
JP 49042901	B	18-11-1974	NONE	
JP 5229904	A	07-09-1993	NONE	
US 5885593	A	23-03-1999	NONE	

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/06305

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
JP 2001139993	A	22-05-2001	NONE		
WO 9427436	A	08-12-1994	WO	9427436 A1	08-12-1994
DE 4026756	A	27-02-1992	DE	4026756 A1	27-02-1992
			US	5670160 A	23-09-1997
EP 0339121	A	02-11-1989	US	4804492 A	14-02-1989
			EP	0339121 A1	02-11-1989
			AU	605795 B2	24-01-1991
			AU	8053287 A	12-05-1988
			JP	63165500 A	08-07-1988
			NZ	222226 A	29-01-1990